

Although evaluated from a different perspective, our study also suggests higher rates of anaphylaxis in northern areas of the United States. Previous studies have used epinephrine distribution data, but instead, our study used primary billing diagnostic codes, thus eliminating prescription-writing bias. It has been suggested that this north-south gradient might be due to differences in vitamin D status. Although some studies have shown an inverse relationship between vitamin D status and risk of atopic illnesses,⁹ more studies are needed in this area. Additionally, future studies are needed to evaluate for a north-south gradient for other atopic illnesses, such as asthma, allergic rhinitis, and eczema.

Of note, our study is representative of cases evaluated and treated at freestanding pediatric hospitals. As such, these hospitals are often referral centers providing tertiary care for all children in a certain city or state. It is difficult to assess how this might reflect incidence calculations for the general public. This might overestimate numbers if a large number of difficult anaphylaxis cases are referred to these hospitals. In contrast, it might underestimate incidence because anaphylaxis is an acute illness that is often treated immediately at local smaller hospitals. Also, our method of case identification by means of diagnostic billing codes might lead to errors in incidence calculation if anaphylaxis is inaccurately billed. However, both of these limitations occur in the north and south and should not affect the geographic comparison provided in our study.

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REFERENCES

1. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
2. Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J Allergy Clin Immunol* 2008;122:1161-5.
3. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol* 1999;104:452-6.
4. Simons FE, Sampson HA. Anaphylaxis epidemic: fact or fiction? *J Allergy Clin Immunol* 2008;122:1166-8.
5. Lieberman P, Camargo CA Jr, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol* 2006;97:596-602.
6. de Silva IL, Mehr SS, Tey D, Tang ML. Paediatric anaphylaxis: a 5 year retrospective review. *Allergy* 2008;63:1071-6.
7. Simons FE, Peterson S, Black CD. Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. *J Allergy Clin Immunol* 2002;110:647-51.
8. Camargo CA Jr, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol* 2007;120:131-6.

9. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr* 2007;85:788-95.

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Associations between prenatal pesticide exposure and cough, wheeze, and IgE in early childhood

To the Editor:

Occupational and agricultural studies have reported positive associations between pesticide exposure and wheeze or asthma in adults.^{1,2} Among elementary school children, exposures to herbicides, pesticides, and farm crops in the first year of life, determined retrospectively by questionnaire, were associated with asthma before age 5 years.³ In a prospective birth cohort study in California, having a mother working in agriculture was associated with increased levels of T_H2 cytokines in children at age 2 years.⁴ These associations have not been tested prospectively in children by using measured pesticide levels, nor in an urban cohort, in which residential pesticide use can be widespread.⁵ We hypothesized that measured prenatal levels of pesticide would be associated with greater wheeze and IgE production by age 5 years among inner-city children living in Northern Manhattan and south Bronx.

The Columbia Center for Children's Environmental Health recruited nonsmoking African American and Dominican mothers during pregnancy as described.⁶ The organophosphates chlorpyrifos and diazinon and the pyrethroids *cis*-permethrin and *trans*-permethrin were measured in personal air samples collected from monitors worn by women for 2 days during the last trimester of pregnancy. German cockroach allergen (Bla g 2) in house dust collected prenatally and serum IgE levels (antimouse, antickroach, anti-*Dermatophagoides farinae*, anticat, antidog) at ages 2, 3, and 5 years were assessed by ELISA and ImmunoCAP, respectively, as described.⁷ Prenatal questionnaires provided demographic information, characteristics of the home environment, including exposures to environmental tobacco smoke, and mother's health information. Parental questionnaires administered every 3 months from birth to age 2 years and every 6 months thereafter, and the International Study of Asthma and Allergy in Childhood question regarding asthma over the past year (age 5 years only), were used to derive respiratory symptom categories representing symptoms over the period of the previous 12 months at 2, 3, and 5 years. The mean \pm SD ages of children at the administrations of 2-year, 3-year, and 5-year questionnaires were 2.0 \pm 0.21, 3.1 \pm 0.18, and 5.1 \pm 0.67 years, respectively.

Pesticide and cockroach allergen were modeled as continuous variables after natural log-transformation. A child was considered to have wheezed (or coughed without cold) if there was any report on parental questionnaires of wheeze (or cough without cold) over the past year. A child was considered to be sensitized (dichotomous variable) if any of 5 specific IgEs measured \geq 0.35 IU/mL.⁷ The data were analyzed for cough, wheeze, and sensitization to any of 5 allergens using generalized estimating equations in multivariable models.

We found that pesticide use prenatally (personal home use methods and/or exterminator services) was reported by 87% of families. Eighty-two percent of the homes used pesticides any time postnatally through age 5 years. Table 1 exhibits the

TABLE I. Geometric means (GMs) and percentile levels (ng/m³) of pesticides measured in air

Pesticide	n	GM (ng/m ³) (95% CI)	Percentiles				% > LOD†
			25	50	75	95	
Diazinon	610	11.4 (10.0-13.0)	3.8	10.1	28.0	217	99.8
Chlorpyrifos	612	4.0 (3.6-4.5)	1.7	3.5	9.2	31.1	99.2
cis-Permethrin	607	NC*	<LOD	<LOD	<LOD	1.65	23.0
trans-Permethrin	585	NC*	<LOD	<LOD	0.41	2.48	26.4

*NC, Not calculated because of small percentage above the LOD.

†LOD, Level of detection. Pesticide levels below the LOD were assigned values of one half the LOD.

TABLE II. Associations between prenatal pesticide concentrations in air and health outcomes by age 5

Pesticide	Odds ratios (95% CIs)		
	Wheeze	Cough (without a cold)	Any specific IgE
Chlorpyrifos (n = 338)	0.91 (0.76-1.09)	0.88 (0.72-1.07)	0.78 (0.60-1.03)
Diazinon (n = 337)	0.83** (0.72-0.95)	0.78** (0.67-0.91)	0.64*** (0.50-0.82)
Cis- Permethrin (n = 338)	1.1 (0.86-1.33)	1.3* (1.03-1.56)	0.97 (0.72-1.32)
Trans- Permethrin (n = 323)	1.1 (0.88-1.40)	1.2 (0.93-1.43)	0.95 (0.69-1.32)

Multivariable generalized estimating equation model adjusts for maternal asthma, prenatal environmental tobacco smoke exposure, Bla g 2 level in dust, sex, ethnicity, and age at time of 2-year, 3-year, and 5-year questionnaires.

*P < .05.

**P < .01.

***P < .001.

geometric means and percentile concentrations of pesticides measured in prenatal air samples.

The prevalence of cough for each of the first 5 years of life was 26% (138/539), 21% (121/585), 19% (98/527), 15% (57/381), and 21% (81/379), respectively. In multivariable generalized estimating equation models that controlled for mother's asthma status, prenatal environmental tobacco smoke exposure, sex, ethnicity, child's age when the questionnaire was completed, and cockroach allergen levels (Table II), diazinon was significantly inversely associated with cough by 5 years, whereas *cis*-permethrin was positively associated with cough by 5 years. Although the prevalence of wheeze for each of the first 5 years of life was 40% (261/652), 27% (162/596), 17% (92/529), 18% (67/381), and 63% (85/134), respectively, of the pesticides tested, only diazinon had a significant association with wheeze in the children by age 5 years (Table II).

Also, in our model, controlling for mother's asthma, prenatal environmental tobacco smoke exposure, sex, ethnicity, child's age when the questionnaire was completed, and cockroach allergen levels, an inverse association between diazinon and sensitization to any of the 5 allergens tested at 2, 3, and 5 years was detected (Table II). Finally, cockroach allergen levels were correlated significantly with diazinon ($r = 0.18$; $P < .0001$), *cis*-permethrin ($r = 0.23$; $P < .0001$), and *trans*-permethrin ($r = 0.22$; $P < .0001$), but not with chlorpyrifos ($r = 0.06$; $P = .15$).

In sum, whereas higher prenatal levels of *cis*-permethrin were associated with early cough, higher levels of diazinon, paradoxically, were associated with reduced cough, wheeze, and IgE. Regarding the former finding, in animal studies, permethrins have been associated with excitatory neurotoxicity through action on voltage-sensitive sodium channels.⁸ Some pyrethroids have been reported to inhibit both IFN- γ and IL-4 production in *in vitro* studies.⁹ Sensory irritation, most likely caused by repetitive firing of sensory nerve endings,¹⁰ could result in cough. Pyrethroid-containing aerosols reportedly cause chest tightness, difficulty breathing, and cough in patients with asthma.¹¹ However, in these models, it is difficult to distinguish the independent role of

prenatal exposure on later symptoms from the effects of postnatal exposures that may proxy measured prenatal exposures. The reason for the latter finding of statistically significant negative associations between diazinon and early cough and wheeze remains elusive. It did not appear to be attributed to reduced cockroach allergen levels, given the positive correlation between Bla g 2 levels in the dust and pesticide levels in air. A possible explanation for the inverse association between diazinon levels and allergic sensitization is an organophosphate-driven upregulation of T_H1 cytokine production (and thus downregulation of T_H2), some evidence for which comes from previous *in vitro* and animal model studies. Duramad et al¹² found that exposing human whole blood cell cultures simultaneously to low doses of the organophosphate chlorpyrifos (or its metabolite, chlorpyrifos oxon) and to LPS resulted in the production of significantly higher levels of IFN- γ compared with cells receiving LPS alone. Coincubation with dust mite allergen (Der p 1) did not induce additional T_H2 cytokine IL-4 production. In a study in which rats received inhaled doses of the organophosphate insecticide dichlorvos, IFN- γ levels also increased in lung tissue.¹³ However, these findings contrast with those from agricultural communities in California, in which children of mothers employed in agricultural jobs, and thus exposed to (mainly organophosphate) pesticides, were more likely to have an increased T_H2 phenotype by age 2 years.⁴

A limitation of repeated-measures analysis is the assumption that wheeze or allergic sensitization at one age has similar meaning at a later age. Early wheeze can be transient and attributed to viral infections, whereas persistent wheeze is more likely to have an underlying allergic component.¹⁴ Also, early allergic sensitization to indoor allergens may indicate a different phenotype than sensitization at age 5 years. Finally, one cannot rule out statistical effects resulting from multiple comparisons and unmeasured potentially important confounders (eg, traffic exposure, mold, endotoxin, residence in mixed-use buildings, neighborhood-level pest problems). Our results suggest that prenatal exposures to pesticides may influence the risk of early cough,

wheeze, and IgE production. Individual pesticides may differ in regard to risk. Further longitudinal assessments will help determine the clinical significance of the association between prenatal exposure to *cis*-permethrin and organophosphates and the development of respiratory symptoms, allergy, and asthma.

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REFERENCES

- Hoppin JA, Umbach DM, London SJ, Lynch CF, Alavanja MCR, Sandler DP. Pesticides associated with wheeze among commercial pesticide applicators in the Agricultural Health Study. *Am J Epidemiol* 2006;163:1129-37.
- Hoppin JA, Umbach DM, London SJ, Henneberger PK, Kullman GJ, Alavanja MCR, et al. Pesticides and atopic and nonatopic asthma among farm women in the Agricultural Health Study. *Am J Respir Crit Care Med* 2008;177:11-8.
- Salam MT, Li Y-F, Langholz B, Gilliland FD. Early-life environmental risk factors for asthma: findings from the Children's Health Study. *Environ Health Perspect* 2004;112:760-5.
- Duramad P, Harley K, Lipsett M, Bradman A, Eskenazi B, Holland N, et al. Early environmental exposures and intracellular Th1/Th2 cytokine profiles in 24-month-old children living in an agricultural area. *Environ Health Perspect* 2006;114:1916-22.
- Thier A, Erick J, Klossner C. Plagued by pesticides: an analysis of New York State's 1997 pesticide use and sales data. Albany: Environmental Advocates; 1998.
- Whyatt RM, Camann DE, Kinney PL, Reyes A, Ramirez J, Dietrich J, et al. Residential pesticide use during pregnancy among a cohort of urban minority women. *Environ Health Perspect* 2002;110:507-14.
- Donohue K, Al-alem U, Perzanowski M, Chew G, Johnson A, Divjan A, et al. Anti-cockroach and anti-mouse IgE are associated with early wheeze and atopy in an inner city birth cohort. *J Allergy Clin Immunol* 2008;122:914-20.
- Soderlund DM, Clark JM, Sheets LP, Mullin LS, Piccirillo VJ, Sargent D, et al. Mechanisms of pyrethroid neurotoxicity: implications for cumulative risk assessment. *Toxicology* 2002;171:3-59.
- Diel F, Horr F, Borck H, Irman-Florjanc T. Pyrethroid insecticides influence the signal transduction in T helper lymphocytes from atopic and nonatopic subjects. *Inflamm Res* 2003;52:154-63.
- Vijverberg HPM, vanden Bercken J. Neurotoxicological effects and the mode of action of pyrethroid Insecticides. *Crit Rev Toxicol* 1990;21:105-26.
- Salome CM, Marks GB, Savides P, Xuan W, Woolcock AJ. The effect of insecticide aerosols on lung function, airway responsiveness and symptoms in asthmatic subjects. *Eur Respir J* 2000;16:38-43.
- Duramad P, Tager IB, Leikauf J, Eskenazi B, Holland NT. Expression of Th1/Th2 cytokines in human blood after *in vitro* treatment with chlorpyrifos, and its metabolites, in combination with endotoxin LPS and allergen *Der p1*. *J Appl Toxicol* 2006;26:458-65.
- Elia J, Aoki A, Maldonado CA. Regulation of uteroglobin/Clara cell protein expression after acute lung exposure to an organophosphate insecticide. *Histochem Cell Biol* 2003;120:33-9.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133-8.

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A pilot study of equal doses of 10% IGIV given intravenously or subcutaneously

To the Editor:

Patients with primary immunodeficiency disease are most often given immunoglobulin replacement therapy by the intravenous route.¹ Subcutaneous administration offers advantages that may be important for many patients.^{2,3} Because of differences in the pharmacokinetics of IgG given by the subcutaneous versus intravenous route, the Food and Drug Administration required that the area under the curve of serum IgG versus time must be noninferior for IgG given by the subcutaneous compared with the intravenous route.^{4,5} In contrast, European regulators require only that the trough serum IgG levels maintained on steady-state subcutaneous therapy must be higher than those achieved with intravenous therapy given every 3 to 4 weeks.⁶ These requirements result in the suggestion to use 37% more IgG per month for subcutaneous versus intravenous administration in the United States,³ whereas the same dose is suggested for use by both routes in the European

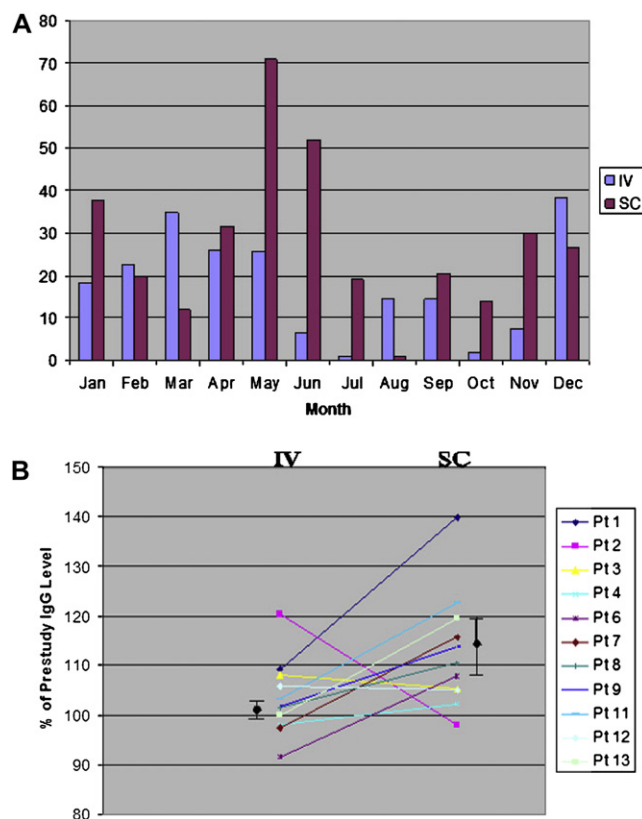


FIG 1. A, Patient days on which symptoms suggestive of infection were reported. The bars represent the total number of days in each month on which subjects reported symptoms of illness, fever, antibiotic treatment, or inability to attend work/school. Any 1 day in the year was counted only once per patient. Because all subjects completed 12 months in the study, the days of risk for all subjects on each route are the same. These data suggest that there was no difference between the number of days of illness in the winter (November-March), 412, and the warmer months (April-October), 415. B, Percentage of prestudy IgG trough level. The figure represents the normalized percentage of prestudy IgG trough level for each patient (Pt) on intravenous (IV) and subcutaneous (SC) therapies, with the prestudy level of each patient set at 100%. Each point represents the mean of 3 determinations in the last 3 months of therapy by each route. The overall mean increase on IV therapy was 1.7% (SD, 5.3), and the overall mean increase on SC therapy was 14.2% (SD, 11.2; $P \leq .004$ by *t* test).